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10/721,693	11/25/2003	William F. Kaemmerer	P-11089.00	3964

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Kenneth J. Collier
Medtronic, Inc.
710 Medtronic Parkway, N.E.
Minneapolis, MN 55432

EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,693	KAEMMERER, WILLIAM F.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-8,16-18,20-22 and 26-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,9-15,19 and 23-25* is/are rejected.

7)☒ Claim(s) *1,5,9-15,19 and 23-25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05, 6/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IV, Claims 5 and 9-25, in the reply filed on August 29, 2005, is acknowledged. The claim set is drawn to a medical system for treating a neurodegenerative disorder, wherein said neurodegenerative disorder is spinocerebellar ataxia type 1. Also acknowledged is applicants' election of single mRNA target, SCA1, which codes for ataxin1 protein; and a single small interfering RNA sequence provided for in SEQ ID Nos: 1 and 2.

The traversal is on the ground(s) that the examiner has not satisfied the requirements of MPEP §803, which states that the inventions must be independent or distinct as claimed and there must be a serious burden on the examiner.

Applicants' arguments have been fully considered but are not found persuasive. The reasons why applicant's original claims were considered to be drawn to independent or distinct inventions have been presented (see the restriction requirement, mailed on July 22, 2005). In that restriction requirement, the examiner grouped applicant's 84 claims into 23 separate inventions. Applicant argues that overlapping subject matter suggests that no search burden exists since many of the groups were classified in the same class and subclass, such as 514/44. However, applicant is reminded that class 514, subclass 44, contains multiple inventions, including many different inventions related to gene therapy, which must be further sorted by keyword and keyword combinations to identify art pertinent to the claimed invention. Furthermore, an adequate search requires both a search and a consideration of the hits.

Applicant is further reminded that the restriction requirement of July 22, 2005, clearly explained that several linking claims were present in the application as filed and that several groups were linked by these claims and that if a linking claim were found allowable (i.e., free of the prior art) linked inventions would be rejoined.

For the reasons given above, and for the reasons stated in the previous restriction requirement, the requirement is still deemed proper and is therefore made FINAL.

Status of the Application

Claims 1–84 are pending. Claims 2, 3, 4, 6–8, 16–18, 20–22, and 26–84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is noted that in the response to the restriction requirement, applicant withdrew Claim 1; however, Claim 1 is examined herein, since it is considered to be a linking claim, as explained in the previous Restriction Requirement. Furthermore, applicant is advised that the previous requirement for restriction to species (page 19 of the restriction requirement) is hereby withdrawn.

Applicant timely traversed the restriction (election) requirement in the reply filed on August 19, 2005.

Claims 1, 5, 9–15, 19, and 23–25 are examined herein, below.

Priority

It is noted that this application appears to claim subject matter disclosed in Provisional Applications No. 60/444,614, filed Feb. 3, 2003; and 60/429,387, filed Nov. 26, 2002. A

reference to the prior applications must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was

due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

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Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, U.S. Provisional application 60/429,387, upon which benefit is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1, 5, 9–15, 19, and 23–25 of this application. In the instant case, no support was found in provisional application 60/429,387 for claims drawn to medical systems comprising small interfering RNA. The instant application clearly defines small interfering RNA (pages 14-15) as "double stranded RNA agents" that are "used to trigger RNA interference." As ordinarily used in the art, "small interfering RNA" normally refers to double stranded RNAs, which operate by a different biochemical pathway

than ribozymes and antisense (single stranded) RNAs. Thus, antisense, ribozymes, and small interfering RNA are considered to represent distinct molecular agents. The earliest filed priority document in which adequate support is provided for medical systems comprising small interfering RNA is U.S. Provisional application 60/444, 614, filed 2/3/03. If applicant believes that support for claims 1, 5, 9–15, 19, and 23–25, drawn to medical systems comprising small interfering RNA agents, is present in the earlier filed priority document, applicant must, in responding to this Action, point out with particularity, where such support may be found.

Claim Objections

Pursuant to MPEP §608.01(m), Claim 1 is objected to because it contains several periods. According to MPEP 608.01(m) each claim should end with a period, but periods should not be used elsewhere except in abbreviations. Appropriate correction is required.

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Claims 1, 5, 9–15, 19, and 23–25 are objected to because the claims appear to be drawn to a medical device or apparatus, yet the preamble recites a medical "system," which may refer to an apparatus or a method. Thus, it is unclear what Applicant intends to claim: an apparatus for treating or a method for treating. *The American Heritage Dictionary, 3rd Ed*, defines the term "system" as a group of interacting, interrelated elements and as an organized procedure or method. Thus, the term has dual meanings. Accordingly, its use in the preamble of the instant claims makes it unclear what statutory class of invention is being claimed. Although, the body of the instant claims do not recite method steps as such, the statutory class of the invention is not instantly recognizable since the term "system" may be interpreted to include both a "functionally

related group of elements" and "an organized and coordinated method." (*The American Heritage Dictionary, 3rd Ed*). It is suggested that the instant claims be amended to more clearly define the statutory class of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 9–15, 19, and 25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 (US 2005/0048641) in view of Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Copending application No. 10/962,732 and the instant application are both directed to a medical device, or system, for transfusing interfering RNA (siRNA) into tissues and cells in living organisms, including humans. Claim 1 of the instant application recites a medical system for treating a neurodegenerative disorder, comprising an intracranial access device, a mapping means, a deliverable amount of siRNA or vector encoding siRNA, and a delivery means. Claim 9 and 10 limit claim 1 by stating that the access device is a catheter or access port. Claim 19 limits claim 1 by stating that the siRNA targets SCA1 mRNA. Claim 25 limits claim 1 by stating that the delivery means is an infusion pump.

Claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 recite a similar system for delivering small interfering RNA targeted to a gene, SCA1, associated with a neurodegenerative disease. Claim 7, the base claim, recites a system comprising an implantable infusion pump, a reservoir, a fluid comprising an RNAi agent, and a catheter. The implantable infusion pump is defined as being either implantable or external, may have a port into which a needle can be inserted to inject a therapeutic agent, and may further have a catheter, and a catheter port (paragraph 24) for delivering an RNAi agent to a specific location in the brain. Paragraph 29 describes a specific embodiment of the claimed system; namely, intraparenchymal and intracerebroventricular delivery devices (illustrated in Fig. 3) for delivering agents to the brain, and clearly embodies an access port and catheter. Thus, the device claimed by claims 7, 8, 16, 17, and 29 of copending Application No. 10/962,732 may serve to deliver siRNA intracranially to different regions of the brain and is, therefore, considered to encompass "medical systems" such as those claimed in the instant application.

Furthermore, Applicant states on page 28 of the instant application (10/721,693) that "The envisioned route of delivery is through the use of implanted, indwelling, intraparenchymal catheters that provide a means for injecting small volumes of fluid containing AAV or other vectors directly into local brain tissue." On page 29 of the instant application, Applicant states that "...the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579..."

Copending Application No. 10/962,732 does not claim a "mapping means" or means for locating a predetermined location in the brain. However, it would be obvious to one of skill in the art to combine the teachings of copending Application No. 10/962,732 with those of a standard anatomical atlas such as that of Cahill et al. or Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations. These anatomical atlases may serve as a means for mapping predetermined locations in the brain. A review of the List of Structures in the Paxinos et al. reference shows that several of the "predetermined locations" recited in claims 11-13 and 15 are described. These include, the substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the subthalamic nucleus, and the medial (fastigial) cerebellar nucleus. The Atlas of Human Anatomy, by Cahill et al., shows some of alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus, enabling the skilled artisan to position the implantable infusion pump and catheter in a manner that would deliver the siRNA to the desired brain location.

Accordingly, one of skill in the art would conclude that the invention defined in the instantly claimed invention of this application (No. 10/852,997) is an obvious variation of the

invention defined in copending Application No. 10/721,693 since each of the required elements are present and each of the devices or systems is clearly intended to serve as a system for delivering small interfering RNA (specifically siRNA targeting SCA1 mRNA) intracranially to treat a neurodegenerative disease.

Thus in the absence of evidence to the contrary, the instantly claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites "a medical system of claim 1 wherein said small interfering RNA is substantially provided for in any one of SEQ ID Nos: 1–44." In the response to the previous restriction requirement, Applicant elected SEQ ID Nos: 1 and 2.

The phrase "substantially provided for in any one of" is confusing. It is unclear what is meant by "substantially provided for." Thus, the metes and bounds of the claim cannot be determined. A review of the specification finds no clear definition of the phrase, which can have multiple meanings, depending on the context. It is suggested that the claim be amended to more precisely define the small interfering RNA being claimed. For example, "The medical system of

claim 1, wherein said small interfering RNA comprises SEQ ID NO: 1 and SEQ ID NO:2." However, in amending the claim, note the objection above to the use of the word "system."

Additionally, Applicant is required to amend Claim 23 to remove recitations of non-elected inventions SEQ ID Nos: 3–44.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 11–15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010 (cited in IDS); Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed.

Xia et al. teach a method for intracranial delivery of a vector encoding a small interfering RNA (siRNA). Specifically, Xia et al. teach a method for silencing gene expression *in vivo* in the brain of a mouse using a recombinant adenovirus encoding small interfering RNA (page 1007). In a pilot experiment (described on pp. 1007-8), Xia et al. used a virus encoding siRNA specific for green fluorescent protein (GFP) to silence eGFP expression in transgenic mice that express eGFP endogenously in their brain tissue. Xia et al. state that the recombinant virus was "injected" into the brain, specifically the brain striatal region (page 1007, 1010). Thus, Xia et al. delivered the vector directly to the brain by "injection." This is taken to mean that a delivery means, such as a syringe, was used to inject the siRNA-encoding vector into the brains of the mice subjects. The device is therefore considered to have functioned both as "an intracranial access device" and as "a delivery means," as recited in the instant claim. Xia et al. state that the virus also contained a dsRed expression cassette, which allowed for unequivocal localization of the injection site by fluorescence microscopy. Thus, "a mapping means" or means for mapping a "predetermined location in the brain" is also present in the Xia et al. system.

Xia et al. show that GFP expression was reduced in the injected hemisphere only (page 1007). Thus, Xia et al. teach a "system" for reducing gene expression in the brain using a vector encoding a small interfering RNA, specifically, a 21-bp hairpin RNA—i.e., a double stranded, interfering RNA—targeting eGFP (page 1009); and also encoding dsRed, to serve as a "mapping means."

Xia et al. further state that their results support the idea that "hairpin RNA can reduce target gene expression through siRNA-mediated mechanisms." (page 1009, 1st column) and go on to suggest that "One powerful therapeutic application of siRNA would be to reduce

expression of toxic gene products in dominantly inherited diseases such as polyglutamine (polyQ) neurodegenerative disorders." (page 1008, 2nd column) This suggests that one of skill could use siRNA encoding vectors *in vivo* to reduce endogenous gene expression in the brain, as shown by Xia et al. See also page 1009, 2nd column. Thus, Xia et al. clearly teach a system within the scope of Claim 1 that is suitable for treating a neurodegenerative disease using small interfering RNA.

Given the teachings of Xia et al., it is likely that one of skill in the art would be mindful of the teachings of Driscoll et al. (cited in Applicant's IDS), who teach methods for making and using vectors encoding short hairpin RNAs targeting genes associated with neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease (pages 3-5; 41-46). Exemplary vectors are illustrated in Figs. 5 and 6. One vector in particular, expresses an inverted repeat sequence specific for alpha synuclein, a gene associated with Parkinson's gene. Figs. 1 and 2 outline the procedure and principles for preparing and using said shRNA expressing vectors to inhibit gene expression. The expressed RNAs are predicted to form hairpin RNAs, having double stranded structures that mediate gene-specific inhibition via an RNAi mechanism. The vectors are said to be useful in the treatment of diseases such as Alzheimer's to reduce plaque formation.

Xia et al. and Driscoll et al. do not teach how to specifically target predetermined locations in the brain. However, one of skill in the art following the Xia et al. teachings would be expected to refer to an anatomical atlas such as that provided by Paxinos et al., who provide not only an anatomical guide of the mouse brain but also stereotaxic coordinates for different brain locations, which may serve as "mapping means," enabling the skilled artisan to locate

predetermined locations in the brain. A review of the List of Structures in the Paxinos et al. reference shows that several of the "predetermined locations" recited in claims 11-13 and 15 are described. These include, the substantia nigra, the cerebral cortex, the hippocampus, the striatum (caudate putamen), the subthalamic nucleus, and the medial (fastigial) cerebellar cortex. The Atlas of Human Anatomy, by Cahill et al., shows some of the alternative recited structures; specifically, Cahill et al. teach the location of the dentate nucleus. The Cahill et al. and Paxinos et al. atlases are considered to be representative of any number of atlases that the skilled artisan might consult to "predetermine" specific locations in the brain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Xia et al., Driscoll et al., Paxinos et al., and Cahill et al. for the reasons given above. Specifically, it would have been obvious to one of skill in the art to inhibit a specific gene target associated with a particular neurodegenerative disorder using an siRNA-encoding vector, as taught by Xia et al. and Driscoll et al. By using the stereotaxic coordinates provided by Paxinos et al. and detailed illustrations shown by Cahill et al., it would have been obvious to the skilled artisan, that said vectors could be used in a direct delivery system such as that taught by Xia et al. to transmit small interfering RNA (e.g., shRNA) to particular brain cells in specific regions of the brain afflicted by the neurodegenerative disease.

One would have been motivated to create and use such vectors because Xia et al. expressly teach that such vectors work to reduce endogenous gene expression and because RNA interference is taught by Xia et al. and Driscoll et al. as having the potential to relieve symptoms associated with neurodegenerative disorders.

Finally, one would have a reasonable expectation of success given that Driscoll et al. expressly describe methods, and give actual examples, for constructing and using shRNA (small hairpin RNA) expressing vectors for purposes of inhibiting the expression of genes associated with neurodegenerative diseases. Further, one of skill in the art armed with such vectors would have a reasonable expectation of success in predetermining a specific location in the brain, given that Paxinos et al. provide specific stereotaxic coordinates and Xia et al. provide a specific working example of how siRNA may be delivered and thereafter localized, or mapped, in the brain.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

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Claims 1, 5, 9, 10, 19, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006–1010; Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; and Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy*, Wiley-Liss, 3rd ed., as applied to claims 1 and 11–15 above, and further in view of Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); and Matilla et al. (1998) *J. Neuroscience* 18:5508-5516.

Claims 1, 9, 10, 19, and 25 are described above. Claim 5 limits claim 1 by stating that the neurodegenerative disorder is spinocerebellar ataxia type 1. Claim 24 limits claim 1 by stating that the delivery means is injection from an external syringe into an intracranial access port.

Xia et al., Driscoll et al., Paxinos et al., and Cahill et al. are relied on for the reasons given above. These references do not specifically teach the use of a catheter or an access port; an siRNA complementary to an mRNA transcript from the SCA1 gene; injection from a syringe into an intracranial access port; or the use of an infusion pump.

Whitesell et al. teach a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats. (pages 4665-6). The rat subjects are described as containing 22-guage steel cannulae stereotactically implanted in the lateral ventricle (page 4666). The cannulae serve as ports, and for purposes of this examination, are considered to also represent catheters, through which labeled antisense oligos were injected by bolus injection with a Hamilton syringe or continuous injection using a miniosmotic pump (page 4666). ("Catheter" is defined by Merriam-Webster OnLine as a tubular medical device for insertion into body cavities to permit injection of fluids.) Whitesell et al. report that their study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligos, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669). Because the oligos were fluorescently labeled, Whitesell et al. were also able to determine, or map, the location and distribution of the perfused oligos.

Davidson et al. teach a method for preparing viral vectors encoding small interfering RNA for use in gene silencing therapy of genes associated with neurodegenerative disorders, including spinocerebellar ataxia type 1 (SCA1) (see esp. paragraphs 180-185). The authors contemplate the use of their invention as a method for reducing the expression of a gene product (paragraph 5) such as that associated with SCA (see claims 23 and 48). Thus, Davidson teach the

construction of siRNA expression cassettes (paragr. 136-156) and siRNA-encoding recombinant viruses (paragr 157-170) for general use *in vivo* via direct delivery to a mouse brain (paragr. 209).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop siRNA encoding vectors, as taught by Xia et al. and Driscoll et al. for direct intracranial delivery into the brains of mice and other organisms to reduce the expression of dominant disease-causing genes such as mutant ataxin-1 to inhibit neurodegeneration associated with spinocerebellar ataxia type 1, as taught by Davidson et al. One of skill in the art would have been appraised of the correlation of ataxin-1 protein and SCA1 based on the teachings of Matilla et al., who teach that a mutant form of ataxin-1 is responsible for the physiological abnormalities associated with SCA1.

One would have been motivated to create such systems for delivering SCA1-targeting small interfering RNA into the brains of mice or rats because Matilla et al. teach that SCA1 has a genetic basis involving the expression of a mutant or toxic form of the SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508).

One would have a reasonable expectation of success given that the combined teachings of Xia et al. Driscoll et al., and Whitesell et al. teach that systems for direct delivery of antisense RNA or vectors encoding siRNA (e.g. short hairpin RNA) can be used effectively to reduce gene expression in brain tissues and that the direct delivery with continuous infusion can result in potentially therapeutic levels and extensive brain uptake of antisense oligos (see Whitesell throughout), circumventing the obstacles observed with systemic administration through the

blood stream. Furthermore, Davidson et al., encourage and teach the use of recombinant siRNA-encoding vectors to treat spinocerebellar ataxia type 1 (SCA1).

Thus in the absence of evidence to the contrary, the invention as a whole as claimed in the instant claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Prior Art not relied upon

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Elsberry (WO 97/40874), who teaches a system for treating neurodegenerative disorders by brain infusion.
- Elsberry et al. (US Patent 5,735,814) and Elsberry et al. (US Patent 5,814,014), who teaches devices for treating neurodegenerative disorders by brain infusion. On page 27 of the intant application, Applicant states that these devices can be used to deliver small interfering RNA in accordance with the present invention.
- McSwiggen (US Patent Application Publication 2003/0190635), who teaches the preparation and use of small interfering RNA against beta secretase (BACE) to treat Alzheimer's disease.
- Powell et al. (US Patent 6,870,030), who teach antisense oligonucleotides for reducing the expression of aspartyl protease 2 (Asp2) for treatment of Alzheimer's disease.

- Dorri et al. (1997) *Exp. Neurology* 147:48-54, who teach a system for injecting antisense oligonucleotides combined with a fluorescent dye into the hippocampus of rats for alteration of neural activity.
- Zhang et al. (1996) *J. Mol. Neuroscience* 7:13-28, who teach a system for injecting FITC-labeled antisense oligonucleotides into the lateral cerebral ventricles of mice.

Conclusion

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

September 21, 2005